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APPLICATION NUMBER: *60/413,882*
FILING DATE: *September 27, 2002*
RELATED PCT APPLICATION NUMBER: *PCT/US03/30611*

By Authority of the
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U.S. PATENT AND TRADEMARK OFFICE
PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. §1.53(b)(2)

Atty Docket. GANDHI 1

INVENTOR(S)/APPLICANT(S)			
LAST NAME	FIRST NAME	MI	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY
GANDHI	Sham		Edmonton, Canada
JIANG	Zi-Hua		Edmonton, Canada
KOGANTY	R Rao		Edmonton, Canada

[ ] Additional inventors are being named on separately numbered sheets attached hereto

TITLE OF THE INVENTION (280 characters max)

SYNTHETIC α-GALACTOSYLCERAMIDE (α-GalCer) MIMICS AS THERAPEUTIC AGENTS

CORRESPONDENCE ADDRESS

Direct all correspondence to the address associated with Customer Number 001444, which is presently

BROWDY AND NEIMARK, P L L C
624 Ninth Street, N.W , Suite 300
Washington, D C 20001-5303

ENCLOSED APPLICATION PARTS (check all that apply)

[X] Specification — Number of Pages 21 — [X] Applicant claims small entity status See 37 C.F.R §1 27

[X] Drawing(s) — Number of Sheets 15 — [ ] Other (specify) _____

METHOD OF PAYMENT (check one)

[X] Credit Card Payment Form PTO-2038 is enclosed to cover the Provisional filing fee of

[ ] $160 large entity [X] $80 small entity

[X] The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number 02-4035

The invention was made by an agency of the United Stated Government or under a contract with an agency of the United States Government

[X] No [ ] Yes, the name of the U S Government agency and the Government contract number are

_____

Respectfully submitted,

BROWDY AND NEIMARK, P L L C

By: _____
Iver P. Cooper
Registration No.: 28,005

Date: September 27, 2002

Synthetic α-Galactosylceramide (α-GalCer) Mimics as Therapeutic Agents

Background of the Invention

Agelasphins, a family of α-Galactosylceramide (α-GalCer, FIG. 1), were originally extracted from marine sponges and found to exhibit potent anti-tumor properties and other therapeutic applications (Natori et al. 1994). One of α-GalCer synthetic analogues, **KRN7000** (FIG. 1) is a promising immunomodulatory agent, which is currently being evaluated for its potential benefits in antitumor and antiinfectious therapies as well as in the prevention of type I diabetes and autoimmune encephalomyelitis. The adjuvant effect of α-GalCer has also been demonstrated with various different immunogens by its ability to strongly enhance antigen-specific $CD8^+$ T cell response (Gonzalez-Aseguinolaza et al. 2002).

α-GalCer and its analogues are known to induce cell proliferation and cytokine production by natural killer (NK) T cells. Recently it was demonstrated that activation of NK T cells by α-GalCer causes bystander activation of NK, B, $CD4^+$, and $CD8^+$ T cells (Gonzalez-Aseguinolaza et al. 2002). A unique property of α-GalCer is its ability to induce both Th1 and Th2 immunity, which is effected by cytokines such as interleukin-4 (IL-4) and interferon-gamma (IFN-γ). Some α-GalCer analogues activate NK T cells, which in turn secrete both IL-4 and IFN-γ. Thus α-GalCer can stimulate both humoral and cellular immunity through the induction of IL-4 (Th2) and IFN-γ (Th1) respectively. Compounds that elicit predominantly or exclusively IL-4 might be useful as therapeutic agents for Th1-mediated autoimmune diseases, such as inflammation, type I diabetic, and multiple sclerosis. On the other hand, compounds that predominantly elicit IFN-γ might be useful in effective vaccine development against intra-cellular pathogens, such as malaria, tuberculosis, and cancers.

Peptide/glycopeptide antigens are processed and presented by antigen presenting cells (APC) through the class I or class II proteins of the major histocompatibility complexes (MHC) to the T cell receptors (TCRs). On the other hand, glycolipid antigens are bound to CD1 molecules and presented to TCR. In the case of α-GalCer, it binds to CD1d molecule and the complex is recognized at picomolar concentrations by the conserved semi-invariant, CD1d-restricted αβ TCR of mouse and human NK T cells (Kawano et al. 1997). The nature and

orientation of the polar head group of α-GalCer molecule are likely to be important for TCR contact, while the nature of the lipophilic group in the ceramide moiety modulates the binding of α-GalCer to CD1d molecule. Collectively, both carbohydrate and ceramide moieties play important roles in the exhibition of biological activities of α-GalCer molecules.

Brief description of the invention

The goal of the present invention is to design novel mimics of α-GalCer that display biological activities similar to their natural counterparts. One of our premises is to build active components such as the carbohydrates, the hydroxymethylene and the amino group that carries a lipid chain, around the central optically active central carbon (FIG.15). In another aspect we have also chosen the derivatives of serine (1) and pentaerythritol (2) to represent the central carbon atom and act as core of biological activity.

In one particular aspect, it is to design new structures that elicit predominantly Th2 cytokine(s), (e.g. IL-4), over Th1 cytokine(s), e.g. (IFN-γ), or vice versa, so that selective modes of immune responses and therapy can be achieved with these compounds as adjuvants to a vaccine. As shown in FIG. 3–11, various α-GalCer mimics were designed. Some of these molecules have been synthesized (FIG. 12– 14) and biologically evaluated. Synthetic strategies have been developed to prepare α-GalCer molecules that contain double bond(s) in the aglycone.

Brief Description of the Figures

FIG. 1

Shows structures of a natural α-GalCer, **AGL-9b**, which was isolated from marine sponge and exhibited potent anti-tumor activity; and a synthetic analogue, **KRN7000**, which is currently being evaluated as a therapeutic agent in clinic.

FIG. 2

Shows various structures being incorporated into ceramides in the design of α-GalCer mimics. Unsaturated fatty acids and fluoro-substituted lipids can modulate the flexibility of the lipid chains, which in turn affect the antigen presentation of these mimics by CD1d molecules to TCR and thus modulate their biological activities. Similarly, di-lipo-fatty acid

and serine-containing fatty acid all contribute to the lipophilic nature of α-GalCer derived therefrom.

FIG. 3

Shows α-GalCer mimics containing unusual *N*-acyl groups on natural sphingosine.

FIG. 4

Shows α-GalCer mimics having unnatural *N*-acyl groups on sphingosine which carries a *E*-4,5-double bond. The *E*-4,5-ene-sphingosine has not been found for natural α-GalCer molecules from marine sponge, but is present in gangliosides from mammalian sources.

FIG. 5

Shows α-GalCer mimics where the galactose is replaced by 2-acetamido-2-deoxy-galactopyranose (GalNAc) and the ceramide carries an unusual *N*-acyl group.

FIG. 6

Shows α-GalCer mimics wherein the core of sphingosine is substituted by a simple serinol.

FIG. 7

Shows α-GalCer mimics wherein the core of sphingosine is substituted by a simple serine. The carboxylic group of serine can be esterified, amidated, or exist as free acid form.

FIG. 8

Shows α-GalCer mimics containing chemically modified sphigosine in that the carbon chain is disrupted by incorporating heteroatoms, e.g., O, NH and S, in the form of ether, ester, or amide linkages.

FIG. 9

Shows α-GalCer mimics containing an amine-substituted pentaerythritol unit to replace the natural sphingosine.

FIG. 10

Shows examples of α-GalCer mimics where divalent galactose is built on the pentaerythritol unit.

FIG. 11

Shows examples of steroidal galactopyranosides derived from plant-originated sterols as potential functional mimics of α-GalCer mimics.

FIG. 12

Shows the synthetic pathway for three α-GalCer mimics, **1**, **2** and **3**, based on serinol.

FIG. 13

Shows the preparation of α-GalCer mimic **4** containing an arachidonic acid moiety.

FIG. 14

Shows the synthetic pathway for α-GalCer mimic **5** and **6** containing *E*-4,5-sphingosine. The method is generally applicable for preparing α-GalCer mimics with double bond(s) in the aglycone moiety.

FIG. 15

Illustrates serinol, serine and pentaerythritol based tetrahedral carbons used in the construction of monovalent and bivalent α-Gal-Ceramide mimics.

References

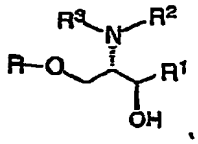
Natori, T.; Morita, M.; Akimoto, K.; Koezuka, Y. *Tetrahedron*, **1994**, *50*, 2771–2784.

Kawano, T. Cui, J.; Koezuka, Y.; Toura, I.; Kaneko, Y.; Motoki, K.; Ueno, H.; Nakagawa, R.; Sato, H.; Kondo, E. et al. *Science*, **1997**, *278*, 1626–1629.

Gonzalez-Aseguinolaza, G.; Kaer, L. V.; Bergmann, C. C.; Wilson, J. M.; Schmieg, J.; Kronenberg, M.; Nakayama, T.; Taniguchi, M.; Koezuka, Y.; Tsuji, M. *J. Exp. Med.* **2002**, *195*, 617–624.

Claims:

1. A structure of the following general specifications:



wherein,

R represents a carbohydrate chosen from hexoses, pentoses, deoxyhexoses, aminohexoses, N-acetyl aminohexoses or sialic acid.

R^1 is a substituent chosen from the following group of structures:

$-CH_2(CH_2)_mCH_3$,

$-CH=CH(CH_2)_mCH_3$,

$-CH(OH)(CH_2)_mCH_3$,

$-CH_2(CH_2)_mCH(CH_3)CH_2CH_3$, and

$-CH(OH)(CH_2)_mCH(CH_3)_2$ where 'm' is an integer of value between 6 to 20.

R^2 is a substituent chosen from the following group of structures:

-H,

$-CH_2(CH_2)_mCH_3$, and

$-CO(CH_2)_mCH_3$ where 'm' is an integer of value between 0 to 30.

R^3 is a substituent chosen from the following group of structures:

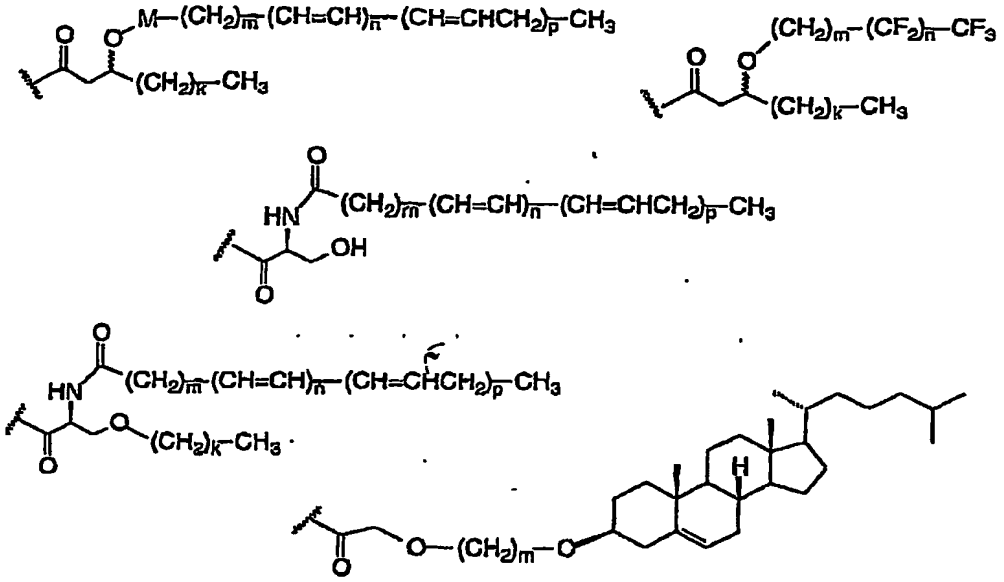
$-CO(CF_2)_mCF_3$,

$-COCF_2(CH_2)_mCH_3$,

$-CO(CH_2)_k(CH=CH)_n(CH_2)_mCH_3$,

$-CO(CH_2)_k(CH=CH\text{-}CH_2)_n(CH_2)mCH_3$, and

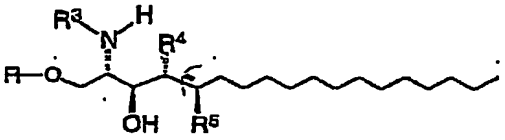
or, a structure of the following group:



wherein,

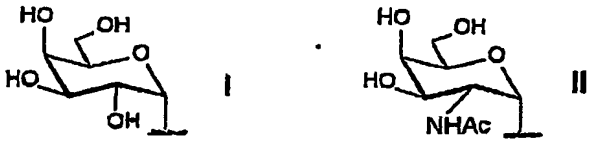
'M' is CH_2 or CO; 'k' and 'm' are independent integers with values from 0 to 30; 'n' and 'p' are independent integers with values from 0 to 10.

2. A compound of claim 1, which is further defined by the following structure:



where,

R is preferably chosen from the following structures I and II.



R^3 is a substituent chosen from the following group of structures:

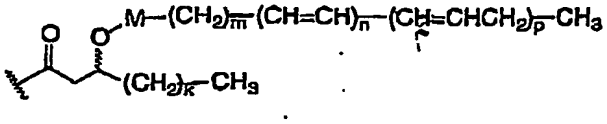
$-CO(CF_2)_mCF_3$,

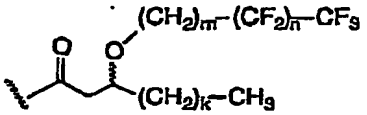
$-COCF_2(CH_2)_mCH_3$,

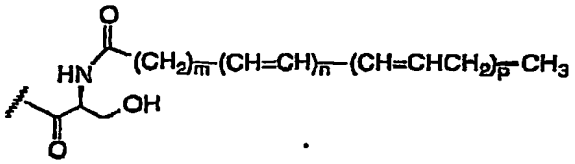
$-CO(CH_2)_k(CH=CH)_2(CH=CH)_n(CH_2)_mCH_3$,

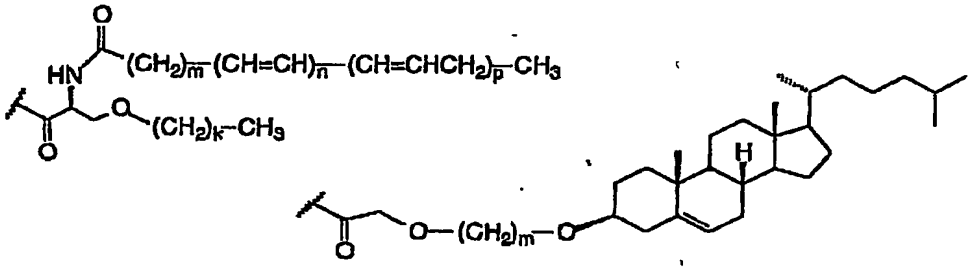
$-CO(CH_2)_k(CH=CH-CH_2)_2(CH=CH-CH_2)_n(CH_2)_mCH_3$.

or, from the following group of structures.







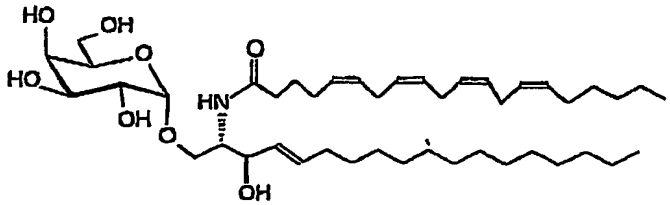


wherein,

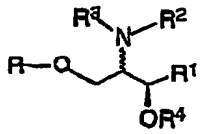
'M' is CH_2 or CO; 'k' and 'm' are independent integers with values from 0 to 30; 'n' and 'p' are independent integers with values from 0 to 10.

R^4 is H or OH, and R^5 is H; or R^4 and R^5 may be flanking groups of a double bond.

3. A compound of claim 2, which is defined by the following specific structure.



4. A compound of the following structure:



where,

R represents a hexose, pentose, deoxyhexose, aminohexose, N-acetylaminohexose or a sialic acid;

R^1 is a substituent chosen from the following general strucutres:

-H,

$-X-Y-Z-(CH_2)_mCH_3$,

$-X-Y-Z-(CH_2)_k(CH=CH)_n(CH_2)_mCH_3$,

$-X-Y-Z-(CH_2)_kCH(OH)(CH_2)_mCH_3$,

where,

'X' and 'Z' are independently CH_2 or CO, and 'Y' is O, NH, or S;
'k' and 'm' are independently integers from 0 to 30 inclusive, and 'n' is an integer between 1 to 10 inclusive;

R^2 is a substituent chosen from the following group of structures:

-H,

$-CH_2(CH_2)_mCH_3$, and

$-CO(CH_2)_mCH_3$

where,

'm' is an integer with values from 0 to 30.

R^3 is a substituent chosen from the following group of strucutres:

$-CO(CH_2)_mCH(OH)(CH_2)_kCH_3$

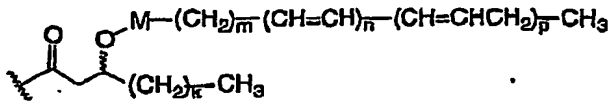
$-CO(CF_2)_mCF_3$,

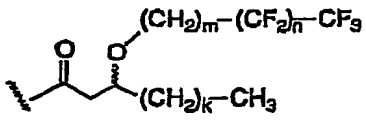
$-COCF_2(CH_2)_mCH_3$,

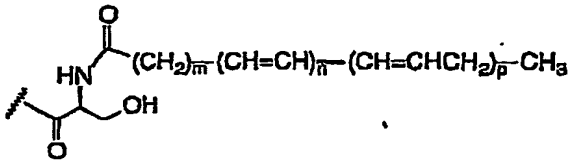
$-CO(CH_2)_k(CH=CH)_n(CH_2)_mCH_3$,

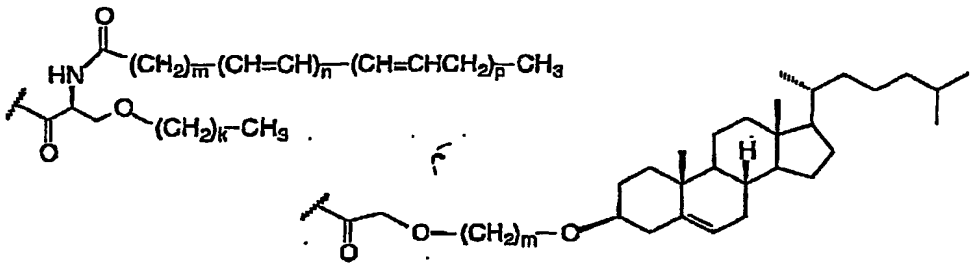
$-CO(CH_2)_k(CH=CH-CH_2)_n(CH_2)_mCH_3$,

or, from the following group of structures:









wherein,

'M' is CH_2 or CO; 'k' and 'm' are independent integers with values from 0 to 30; 'n' and 'p' are independent integers with values from 0 to 10.

R^4 is a substituent chosen from the following group:

-H,

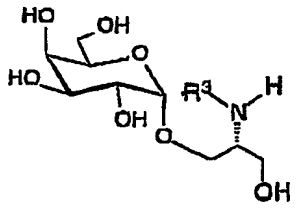
$-M-(CH_2)_mCH(OH)(CH_2)_kCH_3$, and

$-M-CH(CH_2OH)(CH_2)_mCH_3$

where

'M' is CH_2 or CO; 'k' and 'm' are independent integers of values from 0 to 30.

5. A structure according to claim 4 is further specified as follows:



where,

R^3 is a substituent chosen from:

$-CO(CH_2)_mCH(OH)(CH_2)_kCH_3$

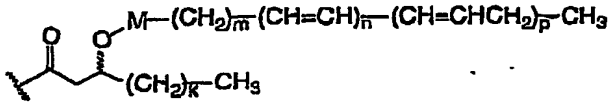
$-CO(CF_2)_mCF_3$,

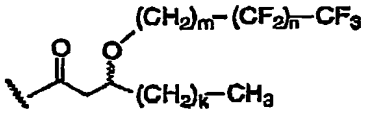
$-COCF_2(CH_2)_mCH_3$,

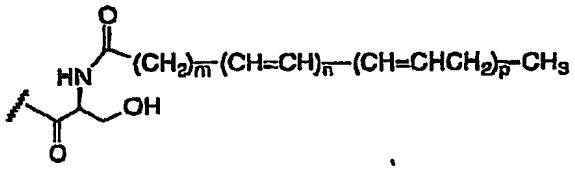
$-CO(CH_2)_k(CH{=}CH)_n(CH_2)_mCH_3$,

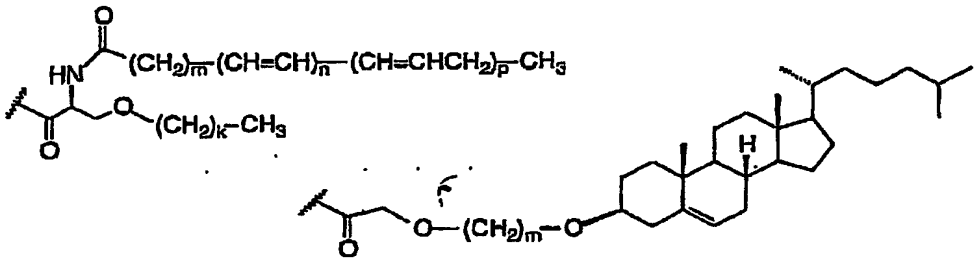
$-CO(CH_2)_k(CH{=}CH\text{-}CH_2)_n(CH_2)_mCH_3$,

or, a structure of the following group:





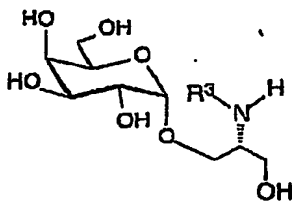




wherein,

'M' is CH_2 or CO; 'k' and 'm' are independent integers with values from 0 to 30; 'n' and 'p' are independent integers with values from 0 to 10.

6. A compound of claim 5 with the following general formula



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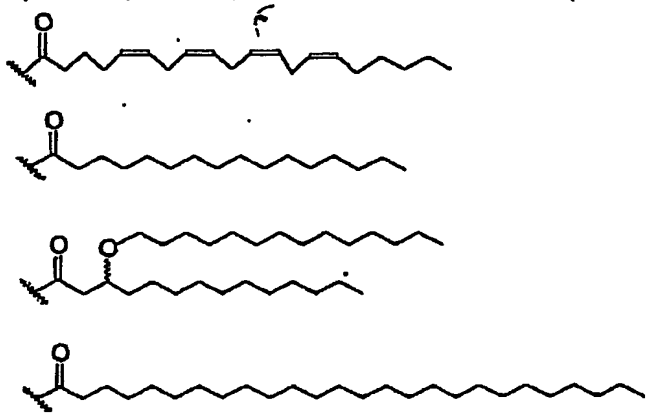
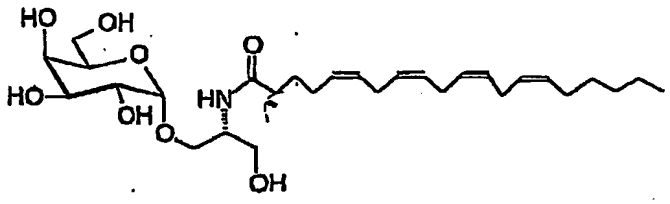
where,

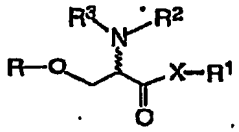
R^3 is a substituent chosen from the following group of structures:



7. A compound of claim 6 that has the following structure:



8. A compound of the following structure:



where,

R represents a a carbohydrate chosen form hexoses, pentoses, deoxyhexoses, aminohexoses, N-acetylaminohexosyl or a sialic acid;

'X' denotes O, NH or S.

R^1 is a substitution group defined by the following:

-H,

$-(CH_2)_k(CH{=}CH)_n(CH_2)_mCH_3$,

$-(CH_2)_kCH(OH)(CH_2)_mCH_3$,

where,

'k' and 'm' are independent integers of values from 0 to 30, and 'n' is an integer of values from 0 to 30.

R^3 is a substituent chosen from the following group:

-H,

$-CH_2(CH_2)_mCH_3$, and

$-CO(CH_2)_mCH_3$

where

'm' is an integer of values from 0 to 30.

R^3 is a substituent chosen from the following group:

$-CO(CH_2)_mCH(OH)(CH_2)_kCH_3$

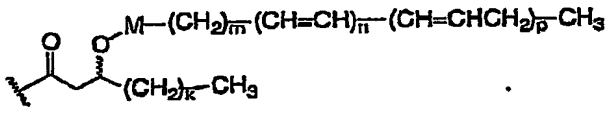
$-CO(CF_2)_mCF_3$,

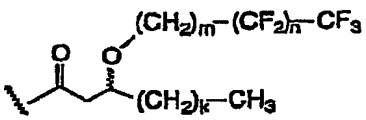
$-COCF_2(CH_2)_mCH_3$,

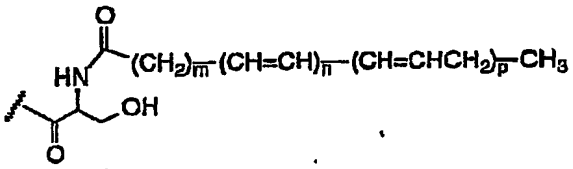
$-CO(CH_2)_k(CH=CH)_n(CH_2)_mCH_3$,

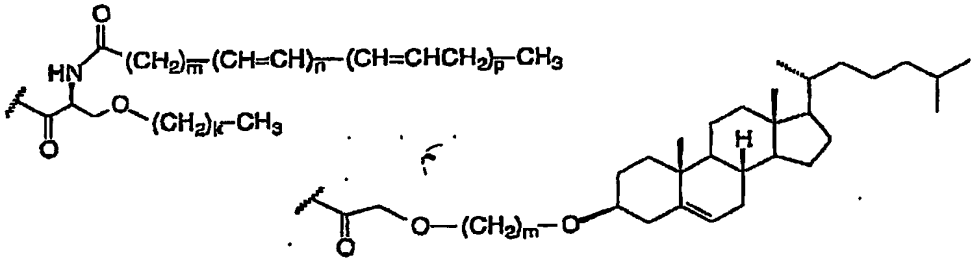
$-CO(CH_2)_k(CH=CH-CH_2)_n(CH_2)_mCH_3$,

or, a structure from the following group:





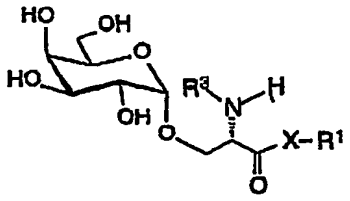




wherein,

'M' is CH_2 or CO; 'k' and 'm' are independent integers with values from 0 to 30; 'n' and 'p' are independent integers with values from 0 to 10.

9. A compound according to claim 8 with a structure of the following specifications:



where,

'X' denotes O, NH or S.

R^1 is a substituent defined by one of the following specifications:

-H,

$-(CH_2)_k(CH=CH)_n(CH_2)_mCH_3$,

$-(CH_2)_kCH(OH)(CH_2)_mCH_3$,

where,

'k' and 'm' are independent integers of values from 0 to 30 and 'n' is an integer of value from 0 to 30.

R^3 is a substitution group chosen from:

$-CO(CH_2)_mCH(OH)(CH_2)_kCH_3$

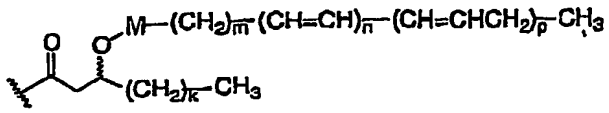
$-CO(CF_2)_mCF_3$,

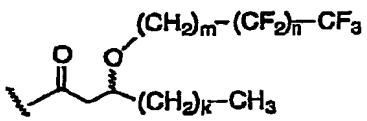
$-COCF_2(CH_2)_mCH_3$,

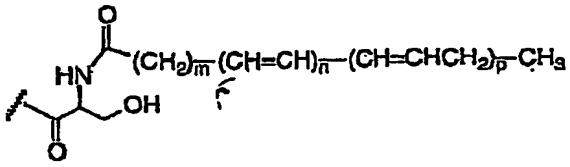
$-CO(CH_2)_k(CH=CH)_n(CH_2)_mCH_3$,

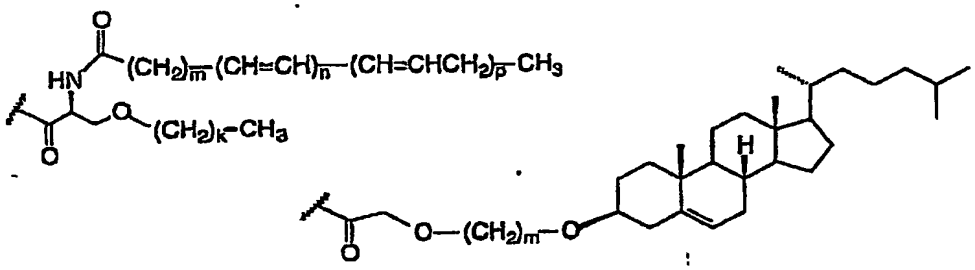
$-CO(CH_2)_k(CH=CH\text{-}CH_2)_n(CH_2)_mCH_3$,

or a structure from the following group:





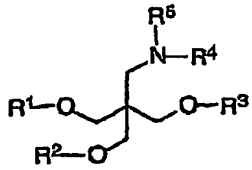




wherein,

'M' is CH_2 or CO; 'k' and 'm' are independent integers with values from 0 to 30; 'n' and 'p' are independent integers with values from 0 to 10.

10. A compound of the following general structure:



where,

R^1 and R^2 independently represent a hydrogen or a carbohydrate such as a hexose, pentose, deoxyhexose, aminohexose, N-acetylaminohexose or a sialic acid.

R^3 is a substituent chosen from the following group:

-H,

$-(CH_2)_mCH_3$,

$-CO(CH_2)_mCH_3$,

$-CO(CH_2)_k(CH=CH)_n(CH_2)_mCH_3$,

$-CO(CH_2)_k(CH=CH-CH_2)_n(CH_2)_mCH_3$,

$-(CH_2)_kCH(OH)(CH_2)_mCH_3$,

$-CO(CH_2)_kCH(OH)(CH_2)_mCH_3$,

where,

'k' and 'm' are independent integers of values from 0 to 30 and 'n' is an integer of values from 1 to 10.

R^4 is a substitution group chosen from:

-H,

$-CH_2(CH_2)_mCH_3$, and

$-CO(CH_2)_mCH_3$

where,

'm' is an integer of values from 0 to 30.

R^5 is a substituent chosen from:

$-CO(CH_2)_mCH_3$,

$-CO(CH_2)_mCH(OH)(CH_2)_kCH_3$

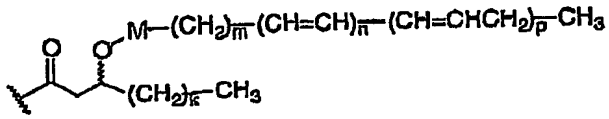
$-CO(CF_2)_mCF_3$,

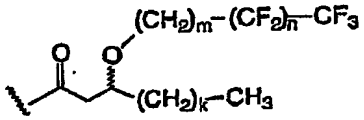
$-COCF_2(CH_2)_mCH_3$,

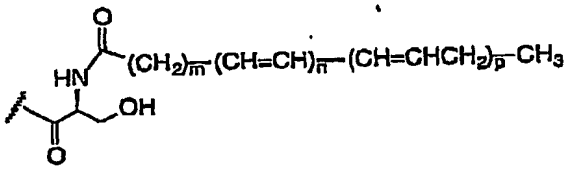
$-CO(CH_2)_k(CH=CH)_n(CH_2)_mCH_3$,

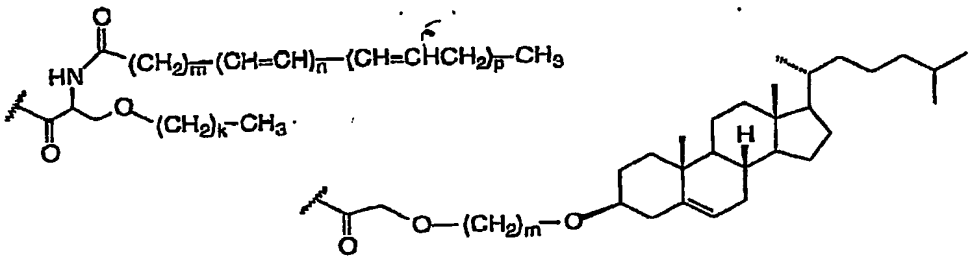
$-CO(CH_2)_k(CH=CH-CH_2)_n(CH_2)_mCH_3$,

or a structure of the following group:





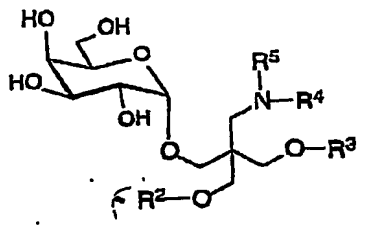




wherein,

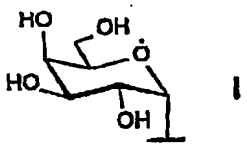
'M' is CH_2 or CO; 'k' and 'm' are independent integers with values from 0 to 30; 'n' and 'p' are independent integers with values from 0 to 10.

11. A compound according to claim 10 where a structure is further defined by the following specifications:



where,

R^2 is hydrogen or α-D-galactopyranosyl residue (I),



I

R^3 is a substituent chosen from the following:

-H,

$-(CH_2)_mCH_3$,

$-CO(CH_2)_k(CH{=}CH)_n(CH_2)_mCH_3$,

$-CO(CH_2)_k(CH{=}CH\text{-}CH_2)_p(CH_2)_mCH_3$,

$-(CH_2)_kCH(OH)(CH_2)_mCH_3$,

$-CO(CH_2)_kCH(OH)(CH_2)_mCH_3$,

where,

'k' and 'm' are independent integers of values from 0 to 30 and 'n' is an integer of values from 0 to 10.

R^4 is a substitution group chosen from:

-H,

$-CH_2(CH_2)_mCH_3$, and

$-CO(CH_2)_mCH_3$

where.

'm' is an integer of values from 0 to 30.

R^5 is a substitution group chosen from:

$-CO(CH_2)_mCH(OH)(CH_2)_kCH_3$

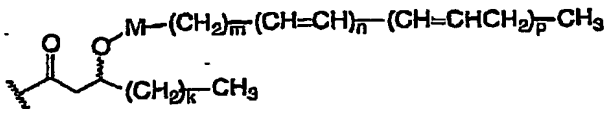
$-CO(CF_2)_mCF_3$,

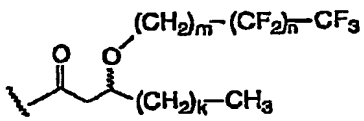
$-COCF_2(CH_2)_mCH_3$,

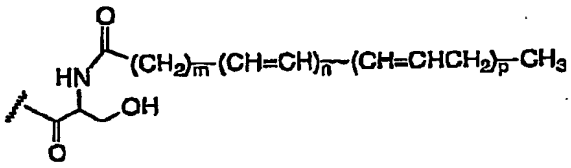
$-CO(CH_2)_k(CH=CH)_n(CH_2)_mCH_3$,

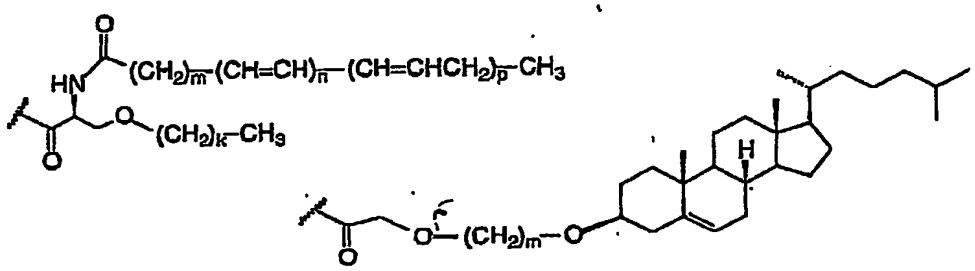
$-CO(CH_2)_k(CH=CH-CH_2)_n(CH_2)_mCH_3$,

or a structure of the following specifications:





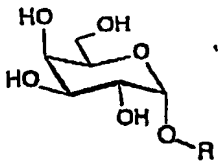




wherein,

'M' is CH_2 or CO; 'k' and 'm' are independent integers with values from 0 to 30; 'n' and 'p' are independent integers with values from 0 to 10.

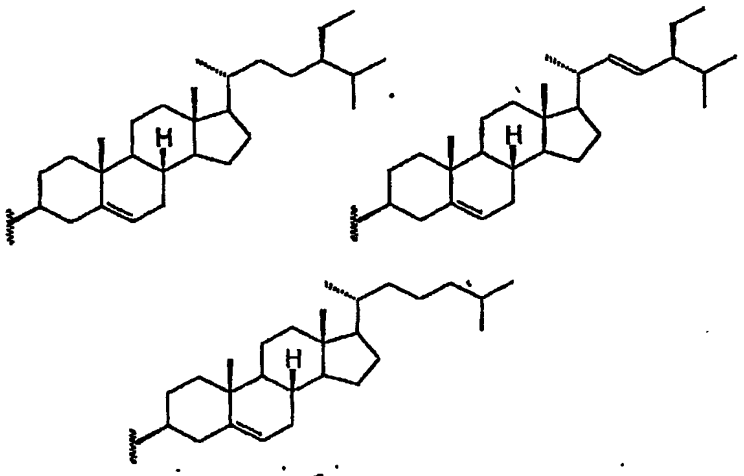
12. A compound of the following structure:



where,

R is a substituent chosen from the classes of compounds designated as steroids, terpenoids, iridoids, sesqiterpenoids, diterpenoids, triterpenoids, or alkaloids.

13. A compound of claim 12 where the steroid group R is chosen from the following:

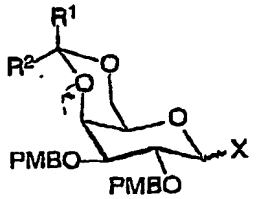


14. The use of compounds in claim 1–13 as therapeutic agents.

15. The use of compounds in claim 1–13 as active ingredient(s) of pharmaceutical composition in liposome formulations.

16. A process of making α-GalCer analogues (mimics) that contain at least one double bond in the aglycone. The glycosylation reaction, in the presence of a Lewis acid as a catalyst, is carried out by the use of the following critical intermediates and results in the formation of the following glycosides:

    a) A glycosyl donor of the following specifications:

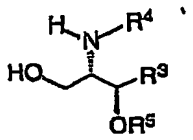


where,

'X' represents a leaving group including, but not limited to, a halogen, $-OC(NH)CCl_3$, -SR, SO_2R, $-O(CH_2)_3CH=CH_2$, $-P(OR)_2$, and $P(O)(OR)_2$ where R represents an alkyl or aromatic group;

R^1 and R^2 are independently a hydrogen atom, alkyl group, or an aromatic group;

b) A glycosyl acceptor of the following specifications:



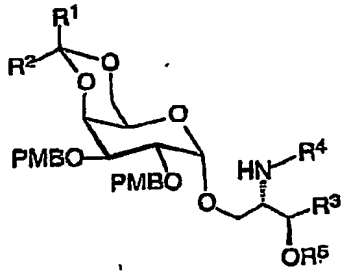
where,

R^3 is an alkyl or alkenyl group, substituted or unsubstituted;

R^4 is an amine protecting group or an fatty acyl group; and

R^5 is a hydroxyl protecting group;

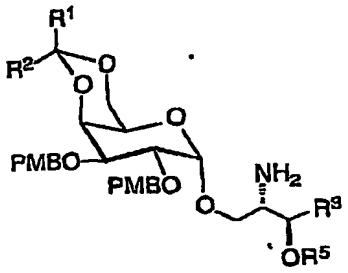
c) A glycoside of the following specifications:



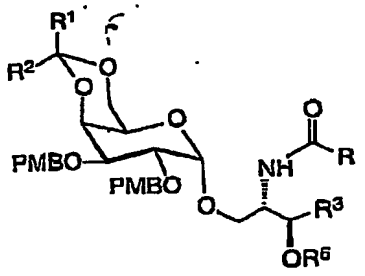
where.

R^1 to R^5 are the same as defined for glycosyl donor and glycosyl acceptor in a) and b).

17. The following amino glycoside which is obtained from the glycoside according to claim 16, by further chemical treatment to exclusively remove the R^4 protecting group.



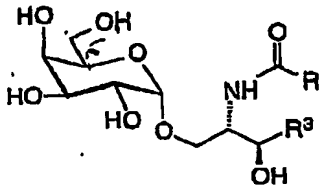
18. A glycoside of the following specification.



where,

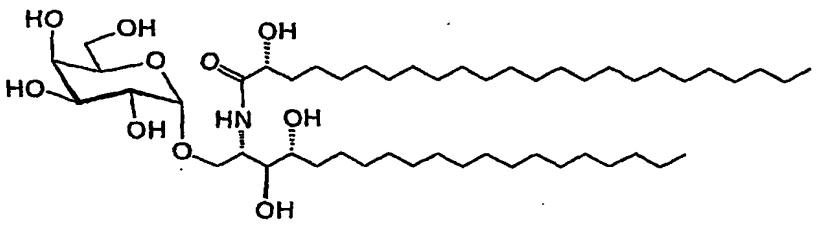
R is an alkyl or alkenyl group, substituted or unsubstituted, and R^1, R^2, R^3 and R^5 are defined as in claim 16.

19. The process of removing protecting groups (R^5, PMB, and R^1R^2CH acetal/ketal at 4,6-*O*-position) of the glycoside of claim 18 in a non-preferential order to yield the following α-GalCer analogue.



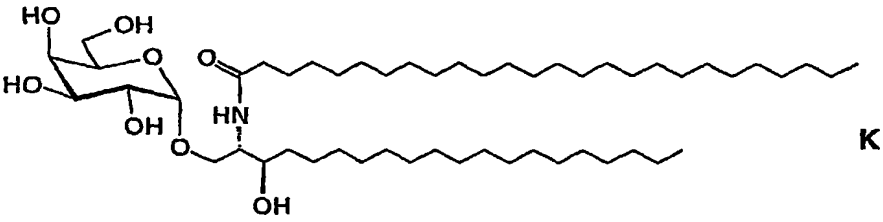
where,

R and R^3 are independent alkyl groups, one or both of which contain at least one double bond.



AGL-9b

Agelaspin-9b (**AGL-9b**) was isolated from marine sponge, *Agelas mauritianus*, and showed antitumor activity against melanoma.

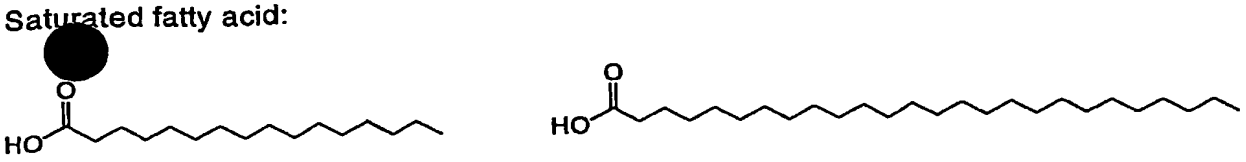


KRN7000

KRN7000 is a synthetic analog of AGL-9b and is currently being evaluated as antitumor and immunomodulating agent in the clinic.

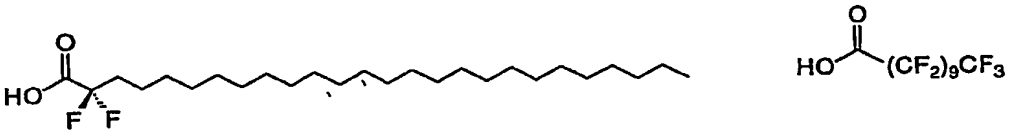
FIG. 1 α-GalCer from natural sources and chemical synthesis as potential immunotherapeutics

Saturated fatty acid:

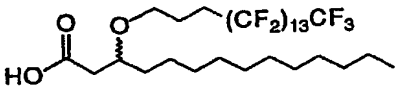


Unsaturated fatty acid:

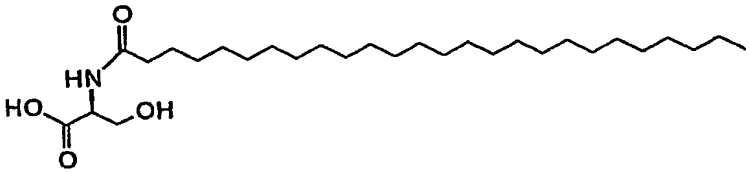
Fluoro-substituted fatty acid::

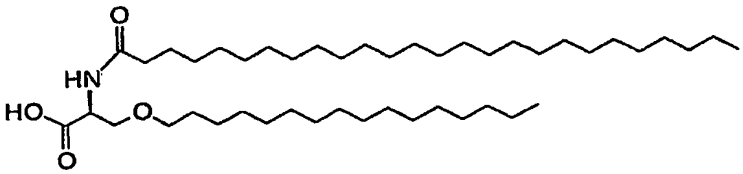


Di-lipo fatty acid::



Serine-containing fatty acid:





Steroid-derived lipo acid:

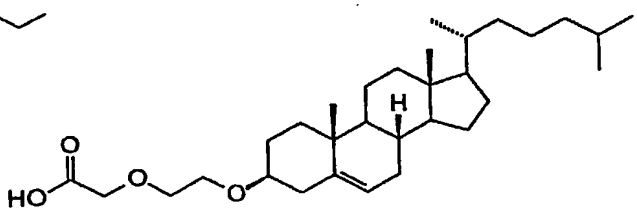


FIG. 2 Structures of fatty acids used in the design of a-GalCer mimics.

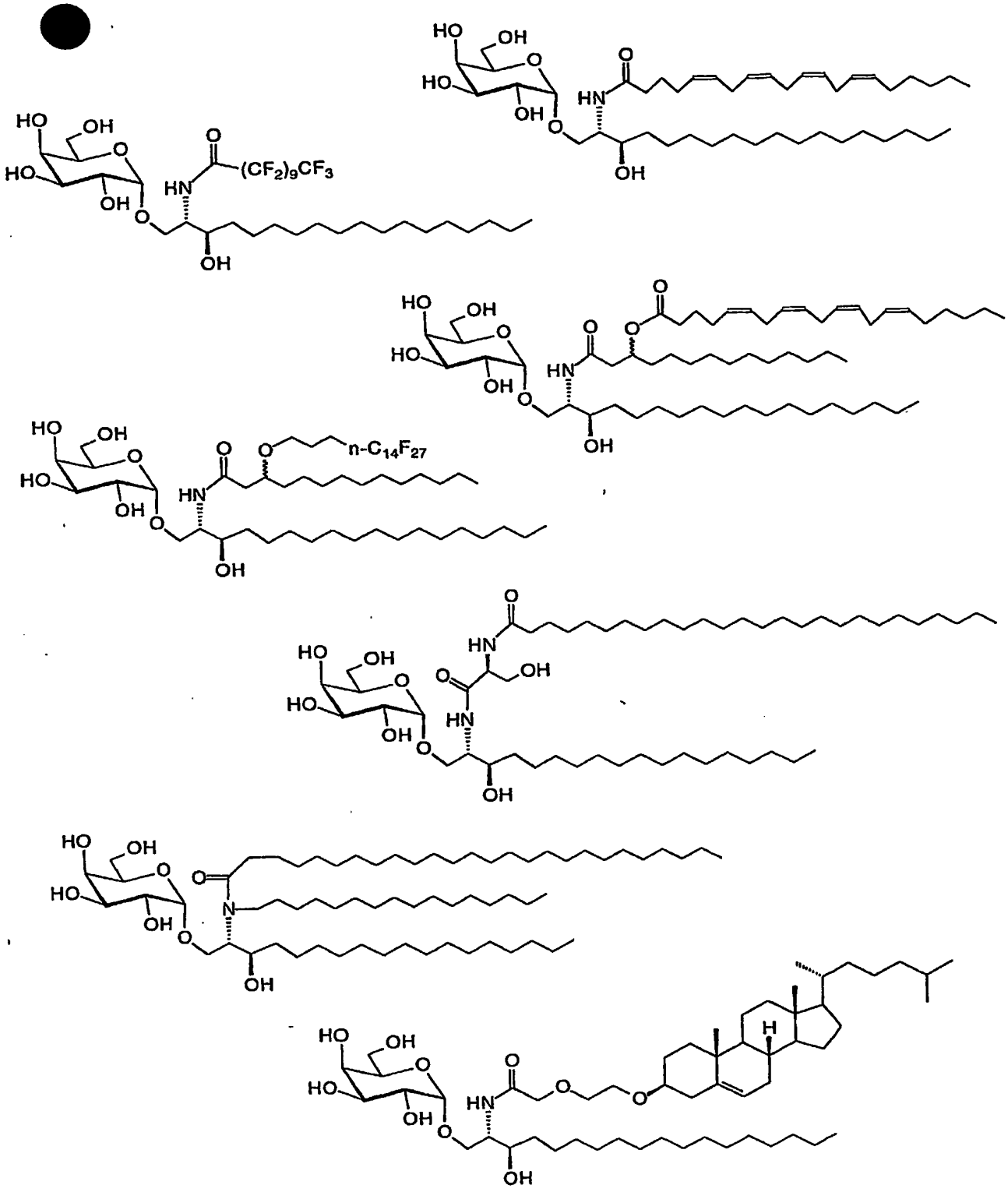


FIG. 3 α-GalCer mimics with modified *N*-acyl group on sphingosine

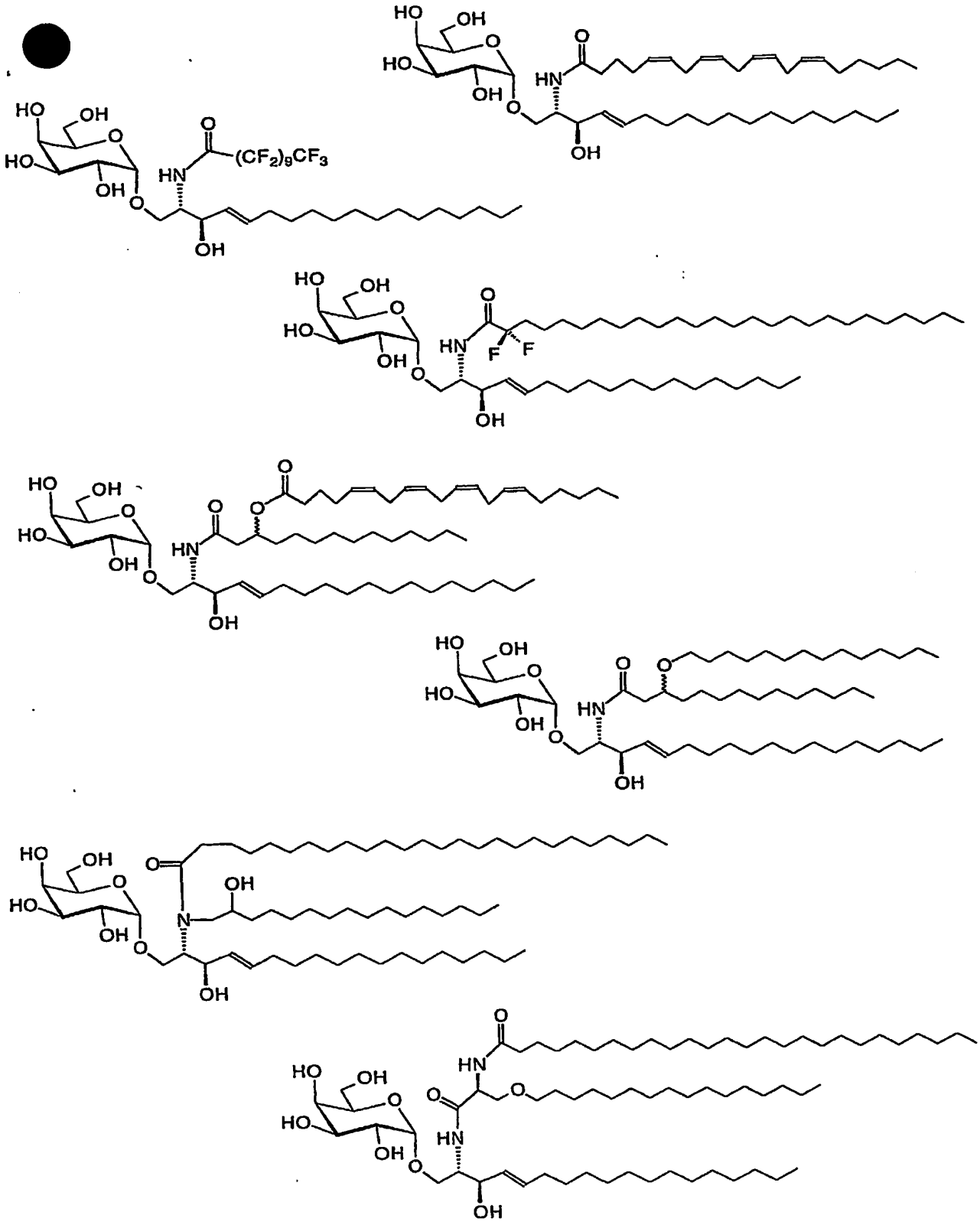


FIG. 4 α-GalCer mimics with *E*-4,5-ene-sphingosine and modified *N*-acyl group

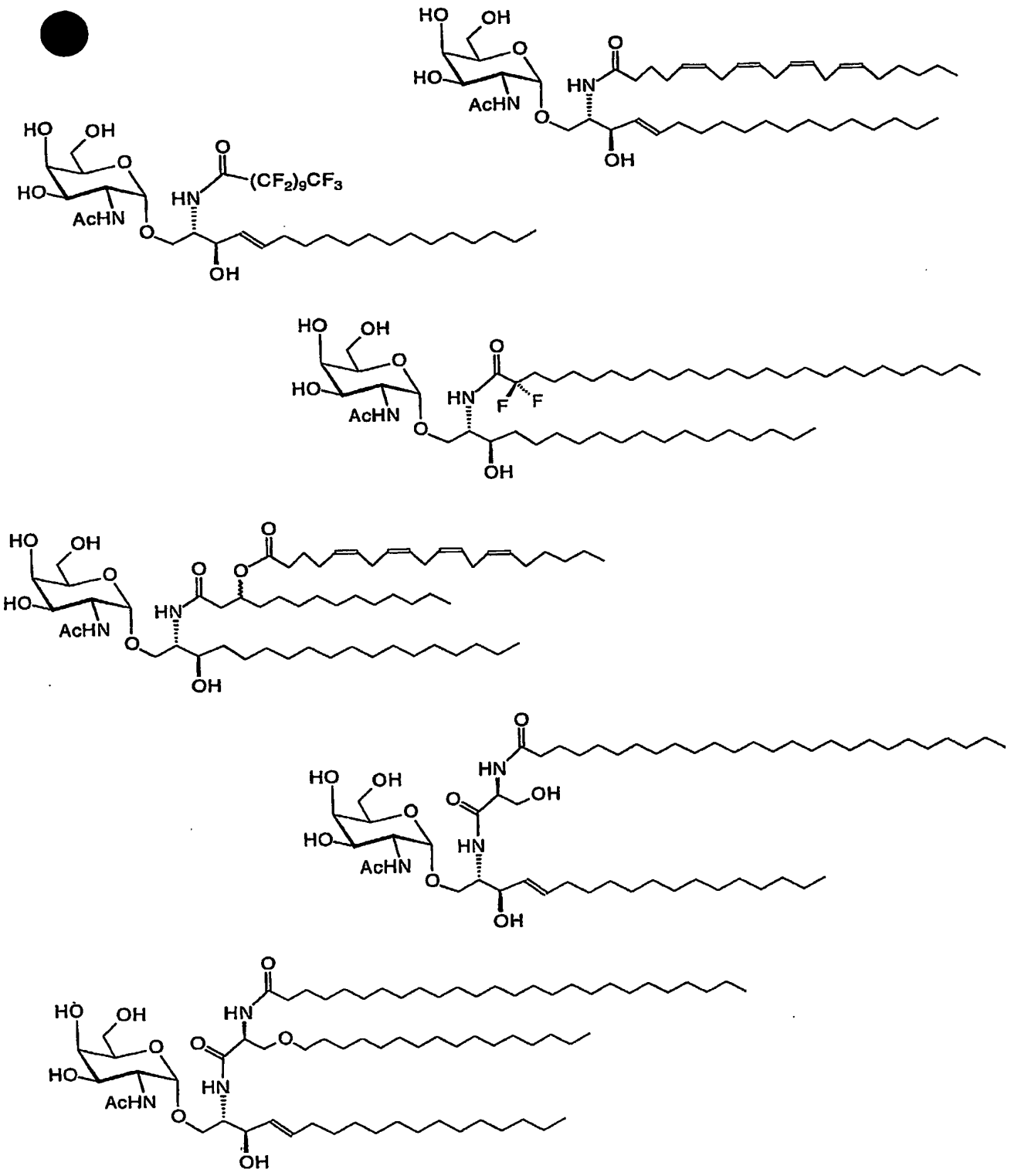


FIG. 5 α-GalCer mimics with GalNAc α-linked to sphingosine carrying modified *N*-acyl group

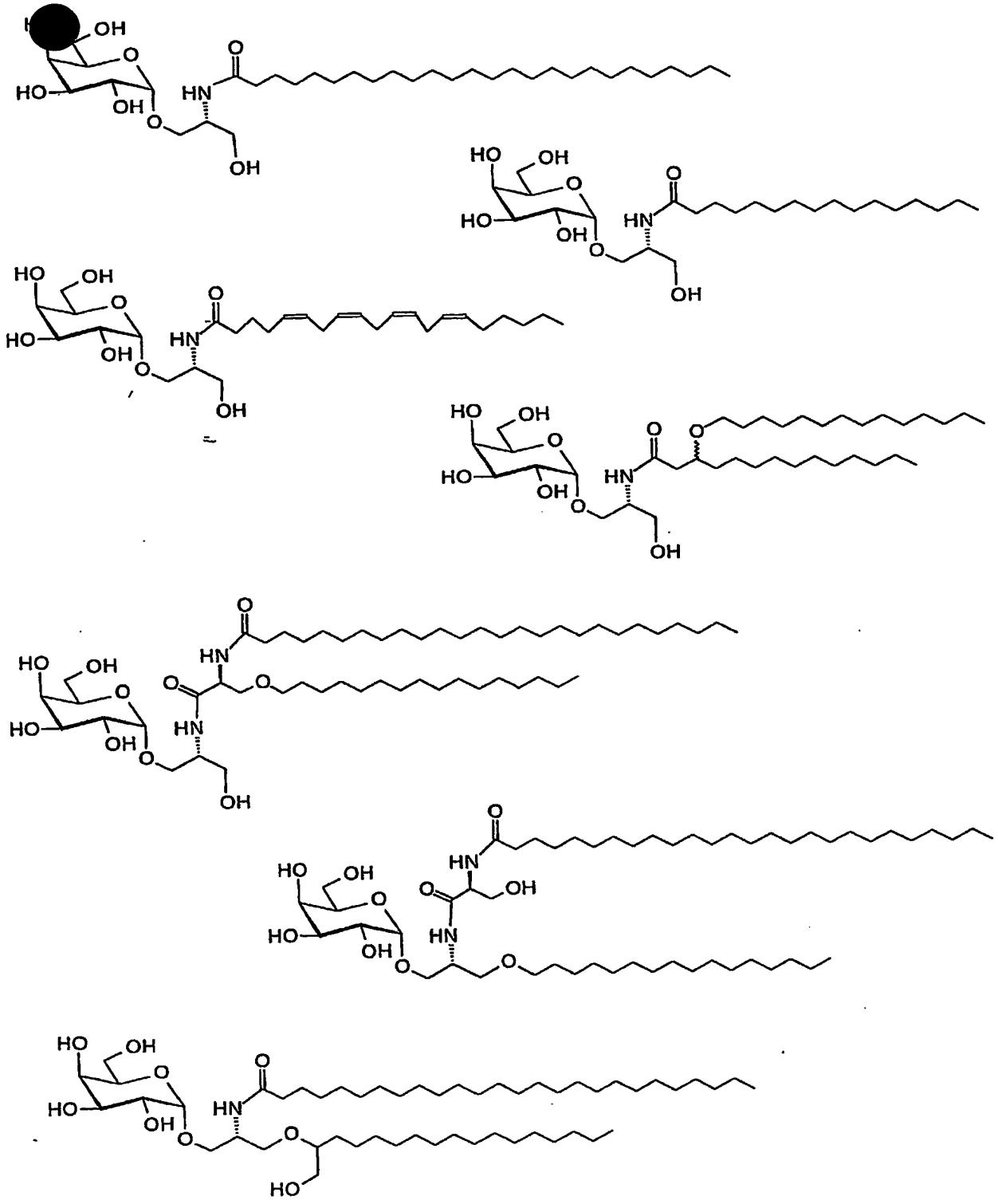


FIG. 6 α-GalCer mimics based on serinol

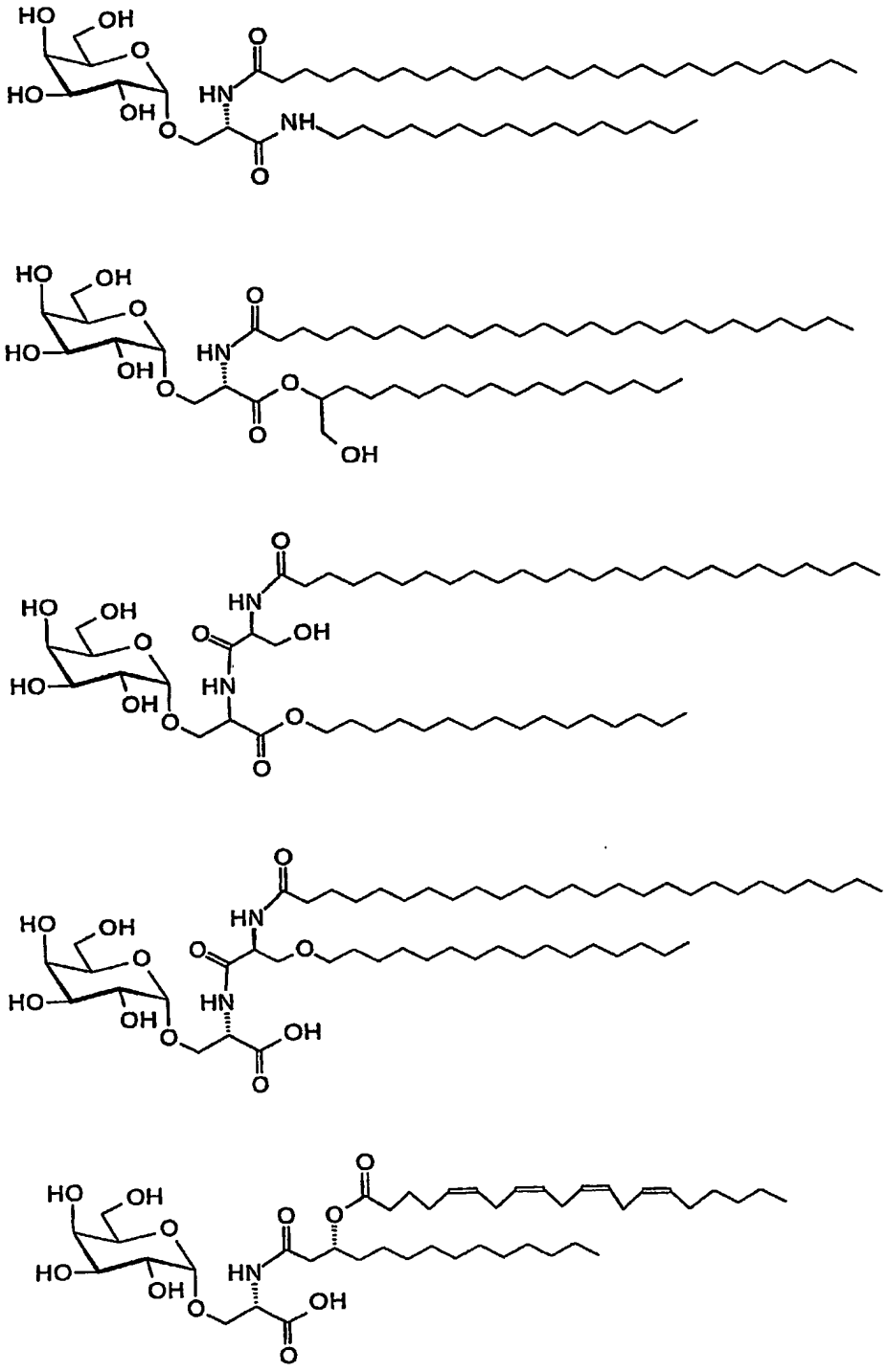


FIG. 7 α-GalCer mimics based on serine

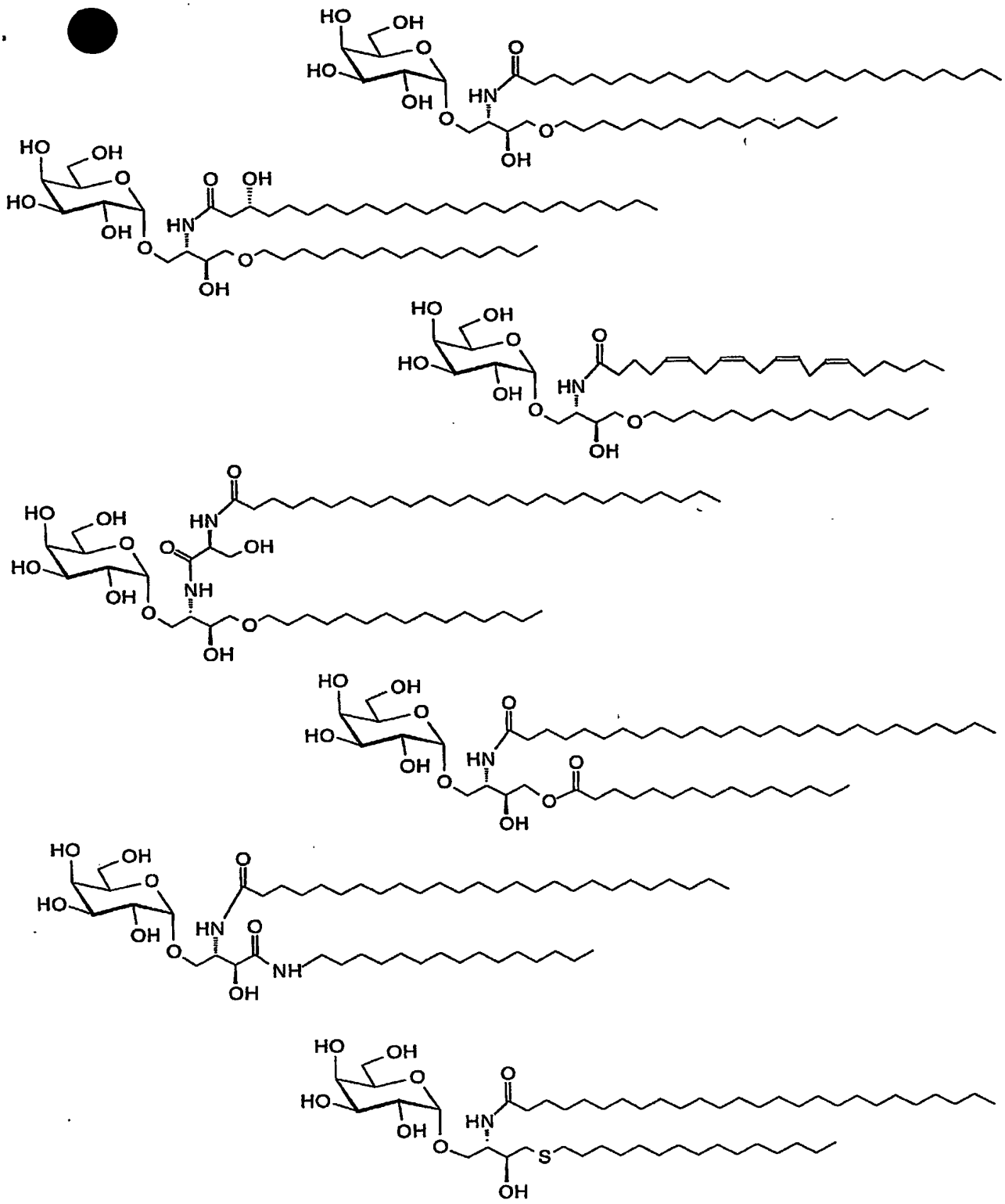


FIG. 8 α-GalCer mimics with modified sphigosine

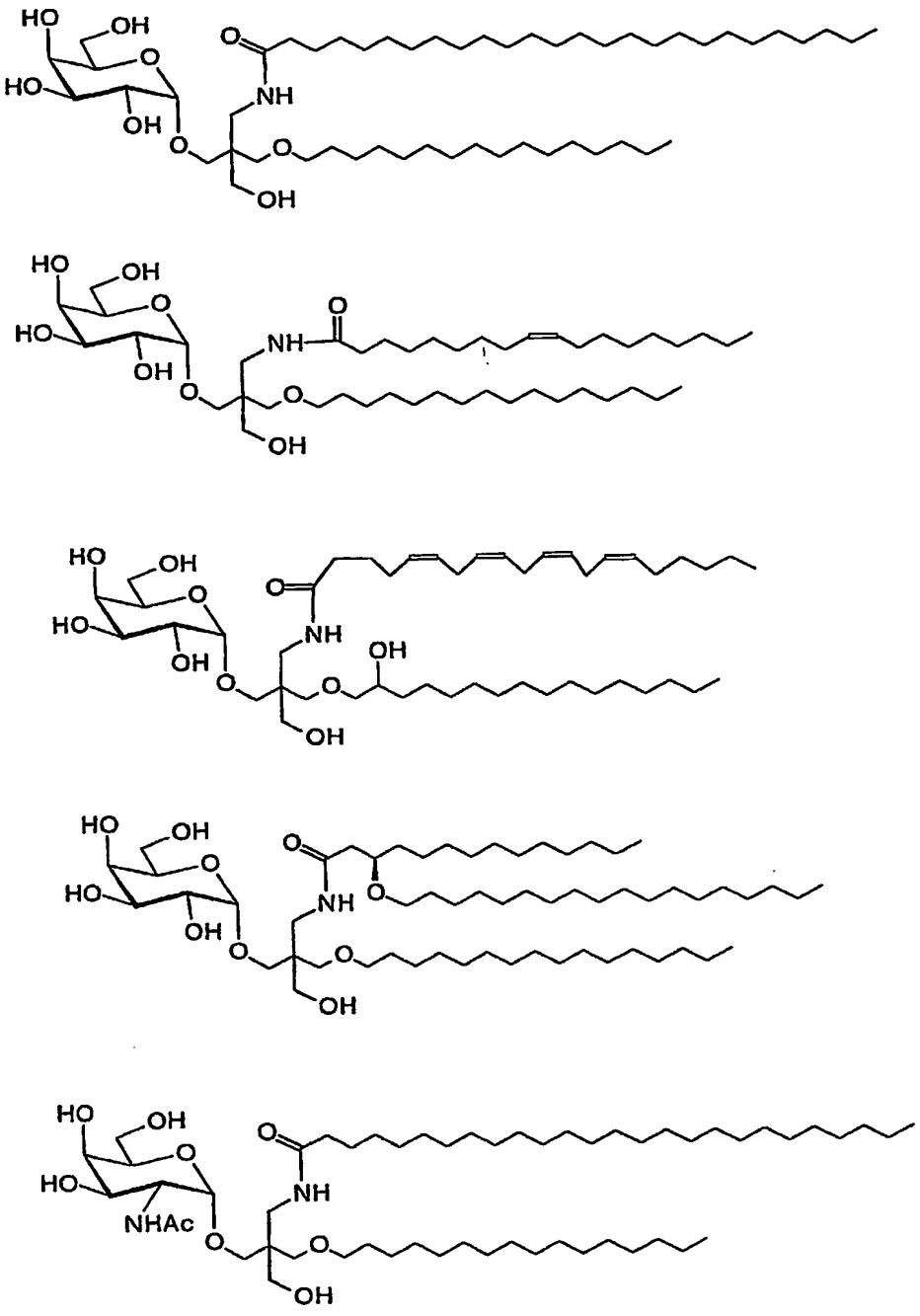


FIG. 9 α-GalCer mimics derived from pentaerythritol

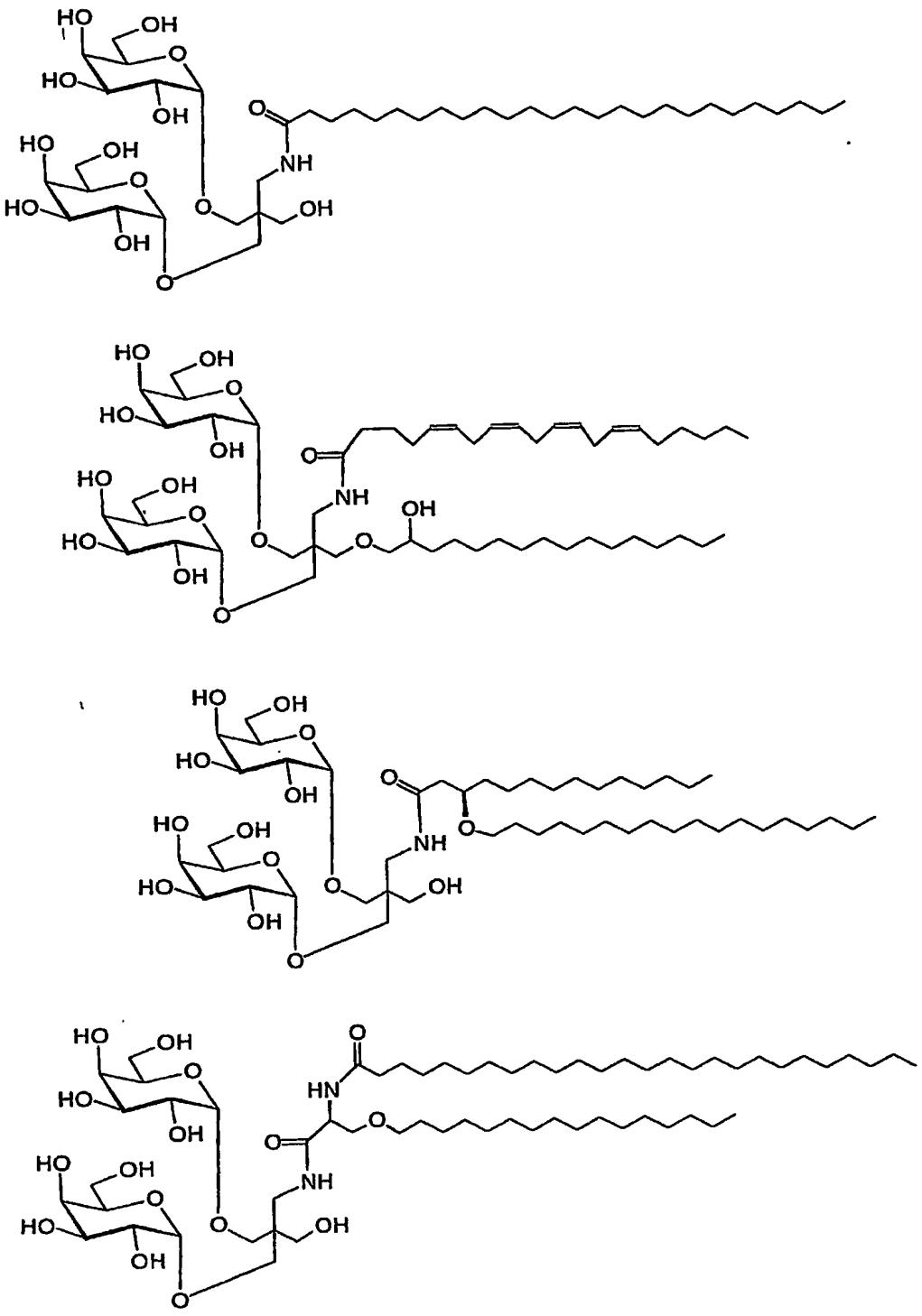
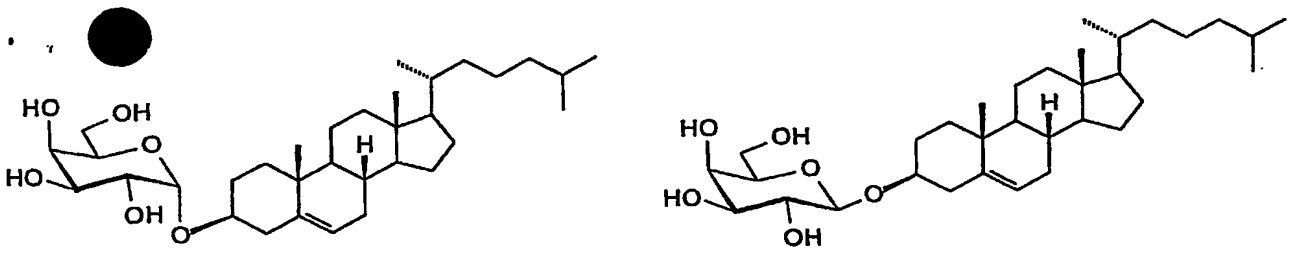
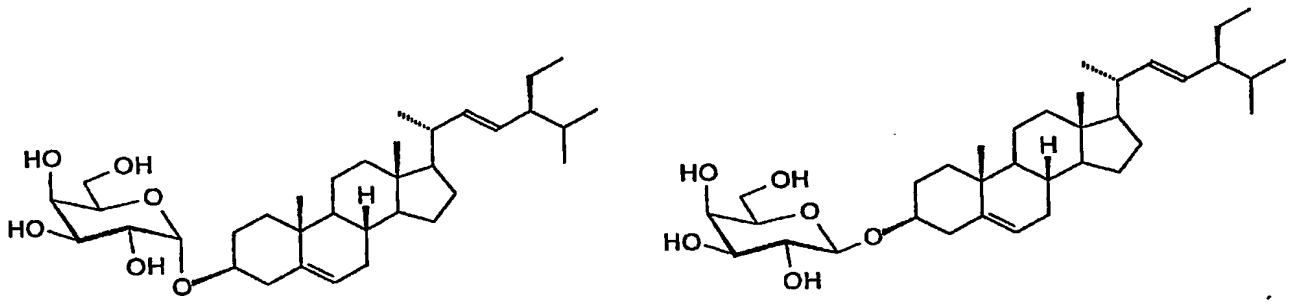


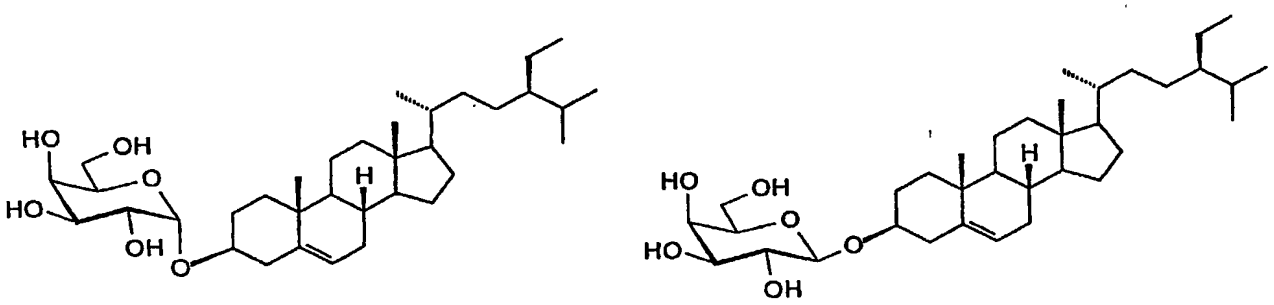
FIG. 10 Divalent α-GalCer mimics derived from pentaerythritol



3-O-(α/β-galactopyranosyl)-cholesterol



3-O-(α/β-galactopyranosyl)-stigmasterol



3-O-(α/β-galactopyranosyl)-sitosterol

FIG. 11 Steroidal galactoside (GalSterol) as functional mimic of α-GalCer

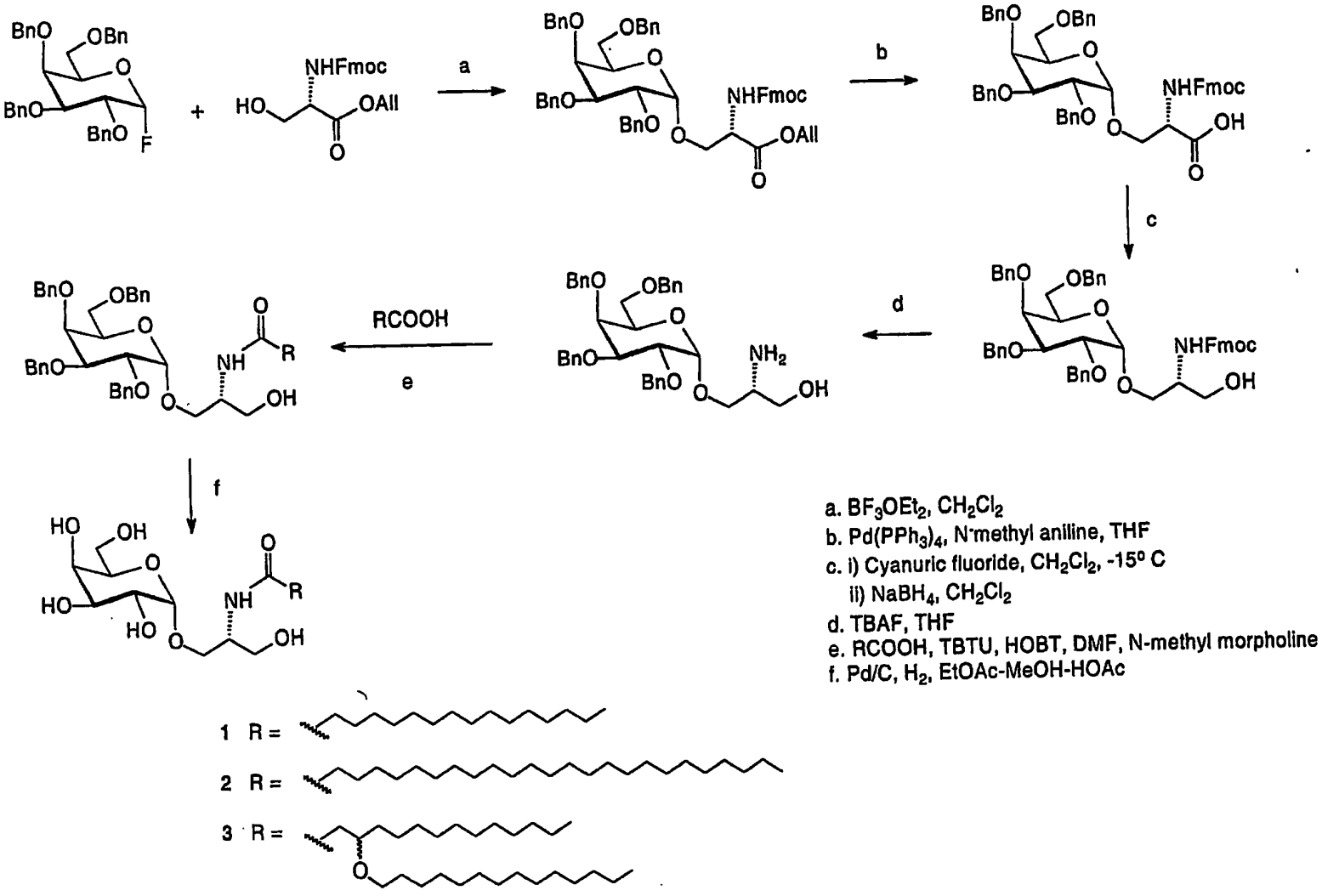
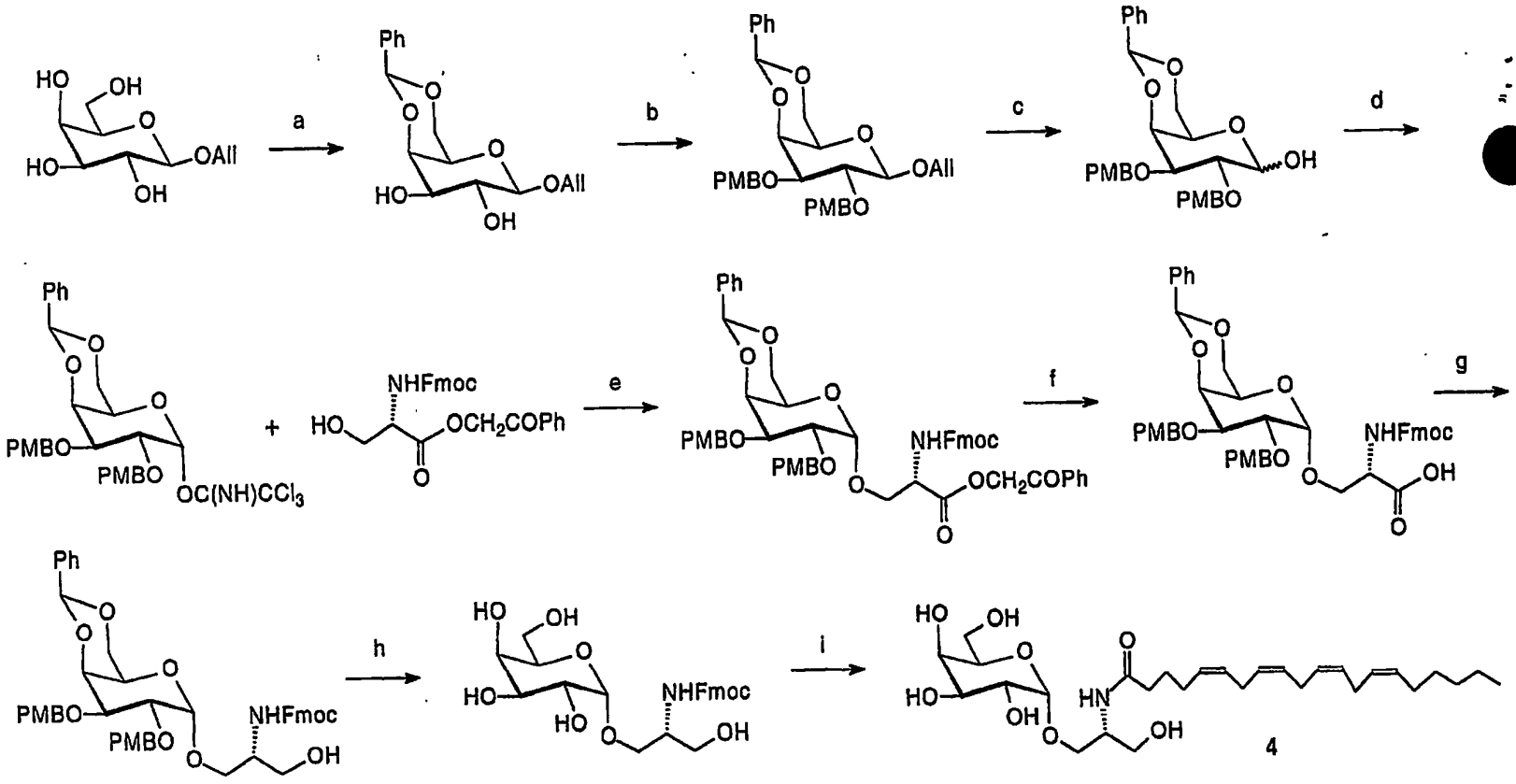


FIG. 12 Preparation of α-GalCer mimics based on serine



a. $PhCH(OMe)_2$, p-TsOH, CH_3CN
b. p-MeO-$PhCH_2Cl$, NaH, DMF
c. i) [bis(methyldipheylphosphine)]($_{1,5}$-cyclooctadiene) iridium(I) hexafluorophosphate, THF; ii) NBS, THF-H_2O
d. $CNCCl_3$, DBU, CH_2Cl_2
e. TMFOTf, THF
f. Zn, HOAc
g. i) Cyanuric fluoride, CH_2Cl_2, -15° C; ii) $NaBH_4$, CH_2Cl_2
h. TFA, CH_2Cl_2
i. i) morpholine; ii) arachidonyl succinimide ester, acetone-H_2O

FIG. 13 Preparation of α-GalCer mimics with double bond on lipid

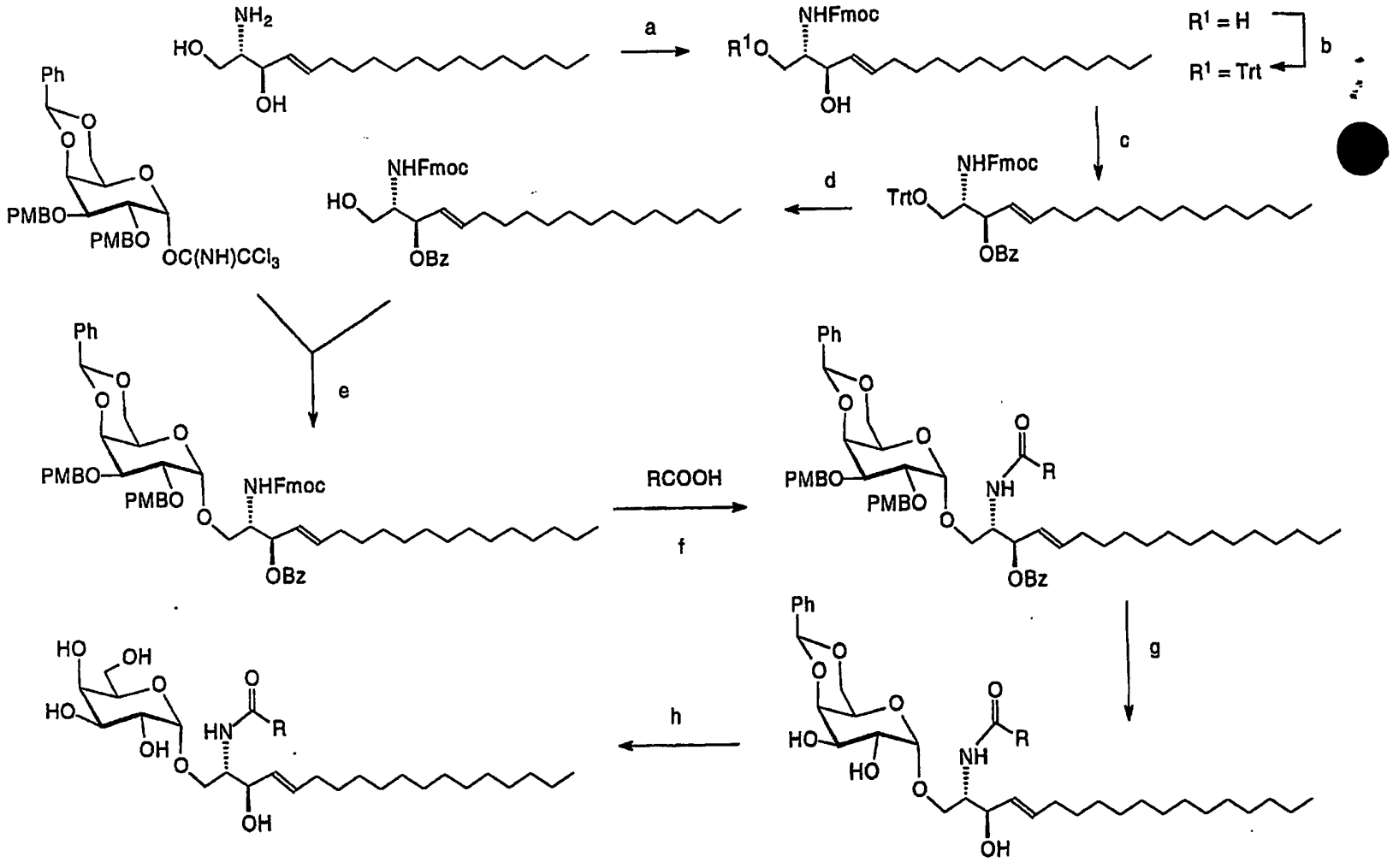
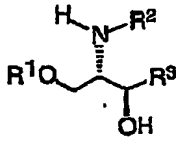


FIG. 14 Preparation of α-GalCer analogues with *E*-4,5-ene-sphingosine



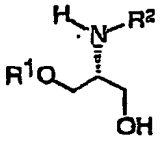
natural α-GalCer

R^1: α-Gal

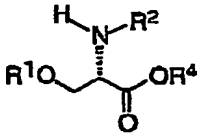
R^2: fattyl acyl

R^3: alkyl

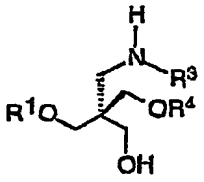
R^4: H, alkyl



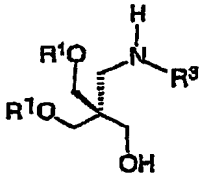
Serinol-based



Serine-based



Pentaerythritol based monovalent



Pentaerythritol based divalent

FIG. 15 Structural features of natural α-GalCer and synthetic mimics